A Once-Weekly R207910-containing Regimen Exceeds Activity of the Standard Daily Regimen in Murine Tuberculosis

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Rationale: **R207910 (TMC207 or J) is a member of the diarylquinolines, a new family of antituberculous drugs with high bactericidal activity when given daily in the murine model of tuberculosis. R207910 exhibits a long half-life and thus is a good candidate for once-weekly therapy of tuberculosis.**

Objectives: **To study the activity of once-weekly R207910 monotherapy and combinations of R207910 with other antituberculous agents (isoniazid, rifapentine, moxifloxacin, and pyrazinamide).**

Methods: **The established infection model of murine tuberculosis was used. Colony counts were determined in the lungs.**

Measurements and Main Results: **Eight weeks of monotherapy reduced the bacillary load by 3 to 4 $\log_{10}$ for rifapentine and by 5 to 6 $\log_{10}$ for R207910 ($P < 0.05$). The addition of rifapentine and isoniazid or moxifloxacin did not improve the bactericidal activity of R207910 monotherapy. In contrast, the triple combination of R207910 plus rifapentine plus pyrazinamide given once weekly for 2 months (i.e., a total of only eight administrations), was significantly ($P < 0.05$) more active than R207910 monotherapy or other R207910 combinations, and led to lung culture negativity in 9 of 10 mice, whereas all lungs were culture positive in the groups treated with other drug combinations. Moreover, R207910 plus rifapentine plus pyrazinamide given once weekly was more active than the current standard regimen of rifampin plus isoniazid plus pyrazinamide given five times per week.**

Conclusions: **The unprecedented activity of the triple combination of R207910 plus rifapentine plus pyrazinamide suggests that it may be feasible to develop a fully intermittent once-weekly regimen.**

Keywords: tuberculosis; animal models; directly observed therapy; R207910; diarylquinolines

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Standard treatment of tuberculosis is long (6 mo) and complicated (daily administration of antibiotics).

What This Study Adds to the Field

This study demonstrates that the diarylquinoline R207910 is active when administrated once weekly in the murine model of tuberculosis. Drug combinations containing R207910 given once weekly are more active than the standard daily regimen.

Tuberculosis (TB) is the most important infectious disease leading to mortality, after AIDS (1). Today, the treatment recommended by the World Health Organization (WHO, Geneva, Switzerland) combines four antituberculous drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) and must be administered daily, largely in the initial 2 months, and at least three times weekly during the continuation phase to achieve a high cure rate (more than 95%). Because of the complexity and length of this treatment, compliance is often unsatisfactory. To improve compliance, WHO recommends that treatment be ingested under the supervision of a health care provider (the so-called directly observed therapy, or DOT) (2). However, daily treatment is difficult to implement in resource-poor countries where the majority of patients with TB are located. Intermittent regimens, ideally given once weekly, would simplify DOT. However, only a single antibiotic, rifapentine, has so far proven to be amendable for once-weekly therapy of TB, and its use is restricted to the continuation phase of treatment of HIV-negative patients who have negative sputum smears at the end of the initial treatment phase (3–5). A companion for rifapentine needs to have a long plasma half-life to allow the development of a once-weekly regimen. Moxifloxacin has proved to be active in the murine tuberculosis model, when administered once weekly with rifapentine and isoniazid, but was also shown to be less sterilizing than standard daily treatment with rifampin plus isoniazid plus pyrazinamide in the intravenously infected mouse model (6). R207910 (TMC 207 or J) is a diarylquinoline that inhibits both drug-sensitive and drug-resistant *Mycobacterium tuberculosis in vitro* through inhibition of the proton pump ATP synthase. The minimal inhibitory concentration (0.06 μg/ml against *M. tuberculosis*) and the natural proportion of resistant mutants in this species (10^{-7} to 10^{-8}) are low (7). When given once daily at 25 mg/kg for 2 months in murine tuberculosis, R207910 is more bactericidal than other available antituberculous drugs (8). R207910 exhibits a long half-life (more than 2 d in the mouse), and its bactericidal effect is maintained for 1 week in mice after a single dose of 100 mg/kg (7). Thus, R207910 seems to be a good candidate to combine with rifapentine for once-weekly therapy of tuberculosis. In this study, we evaluated the bactericidal activity of R207910 alone and in combinations given once weekly in the murine model of tuberculosis.

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METHODS

R207910 (J) was synthesized by Johnson & Johnson (Beerse, Belgium); the other compounds were purchased from the following manufacturers: isoniazid from Laphal (Allauch, France); rifampin, rifapentine, and pyrazinamide from Aventis (Antony, France); and moxifloxacin from Bayer (Puteaux, France). The H37Rv strain of *M. tuberculosis* was prepared as previously described (6). Mice were purchased from the Janvier Breeding Center (Le Genest Saint-Isle, France). For each of the three experiments, 4-week-old female Swiss mice were intravenously infected via the tail vein with 0.5 ml of *M. tuberculosis* H37Rv suspension as follows: 310 mice infected with 5.2×10^6 colony-forming units (CFU) (experiment 1), 110 mice infected with 1.5×10^6 CFU (experiment 2), and 120 mice infected with 6×10^6 CFU (experiment 3). Two weeks postinfection, mice were randomly allocated to treatment groups. In experiment 1, each treated group contained 20 mice and the infected untreated control group contained 30 mice. The mice of the three treated control groups were treated with either rifampin (10 mg/kg, 5 d/wk), isoniazid (25 mg/kg, 5 d/wk), or rifapentine (10 mg/kg, 1 d/wk). The mice of the test groups were treated with R207910 either (*1*) 5 days/week at 6.25, 12.5, or 25 mg/kg, (*2*) twice weekly at 12.5, 25, or 50 mg/kg, (*3*) once weekly at 25, 50, or 100 mg/kg, or (*4*) once every 2 weeks at 50 or 100 mg/kg.

In experiment 2, each treated group contained 16 mice and the infected untreated control group contained 30 mice. All test groups were treated once weekly as follows: groups 2 and 3 were treated with R207910 or rifapentine alone; group 4 was treated with the double combination of R207910 and rifapentine; groups 5 and 6 were treated with a triple combination of R207910 plus rifapentine plus isoniazid or with R207910 plus rifapentine plus moxifloxacin.

In experiment 3, each treated group contained 10 mice and the infected untreated control group contained 40 mice. Except for group 2, which was treated for 5 days/week with the WHO standard treatment of rifampin plus isoniazid plus pyrazinamide, all treated groups were treated once weekly as follows: groups 3, 4, and 5 were treated with R207910, rifapentine, or moxifloxacin alone; group 6 was treated with the double combination of R207910 plus rifapentine; and groups 7, 8, and 9 were treated with the a triple drug combination of R207910 plus rifapentine plus isoniazid, R207910 plus rifapentine plus moxifloxacin, or R207910 plus rifapentine plus pyrazinamide.

Untreated control mice were killed the day after infection (Day −13) and at the start of treatment (Day 0). In experiment 1, 10 mice were killed after 1 and 2 months of treatment in each treated group. In experiment 2, eight mice were killed after 1 and 2 months of treatment in each treated group. In experiment 3, all treated mice were killed after 2 months of treatment. In each experiment, 10 mice were kept for mortality assessment. The animal experiment guidelines of the Faculté de Médecine Pitié-Salpêtrière (Paris, France) were followed.

R207910 was prepared monthly in a hydroxypropyl-β-cyclodextrin solution and kept at 4°C. Other drug suspensions were prepared weekly at the desired concentrations in distilled water containing 0.05% agar and kept at 4°C. All the drugs were given by gavage. In experiments 2 and 3, drugs were given at the following doses: R207910 125 mg/kg weekly, rifampin 10 mg/kg daily, pyrazinamide 150 mg/kg daily or 300 mg/kg weekly, isoniazid 25 mg/kg daily or 75 mg/kg weekly, rifapentine 15 mg/kg weekly, moxifloxacin 400 mg/kg weekly in experiment 2 and 200 mg/kg weekly in experiment 3. Dosing of the drugs was selected to provide areas under the concentration time curve (AUC) in mice that were comparable with those achievable in humans at the usual dosing (6, 7, 9). Moxifloxacin dosing was reduced from 400 to 200 mg/kg between experiments 2 and 3 because new pharmacokinetic data suggested that 200 mg/kg in mice is equipotent to the usual 400 mg/day in human dosing (9).

The severity of infection and the effectiveness of treatments were assessed on the basis of survival rate, spleen weight, gross lung lesions (0, no lesions; +, fewer than 10 tubercles; ++, more than 10 tubercles), and the numbers of colony-forming units in the lungs. Enumeration of colony-forming units and harvesting of lungs were done as previously described (10). Colony unit counts were expressed as mean $\log_{10}$ (CFU) ± standard deviation (SD). Mean colony-forming unit counts were compared by Mann-Whitney test (using Minitab software; Minitab, State College, PA). Differences were considered significant at the 95% level of confidence. Multiple comparisons were done in experiments 2 and 3, and thus adjustment for multiple comparisons was made by means of the Bonferroni correction. In experiment 2, in which there were five test groups, P was adjusted to $P = 0.05/5 = 0.01$. In experiment 3, in which there were eight test groups, P was adjusted to $P = 0.05/8 = 0.006$. Proportions of positive mice after 2 months of treatment were compared by chi-square test (Epi-Info; Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Experiment 1

Survival rate. All untreated control mice died between Day 26 and Day 42 due to the TB infection. All treatments prevented mortality. Fifteen of 310 mice died because of gavage accidents (4.8%): 1 in the isoniazid group, 1 in the R207910 (100 mg/kg 1/7) group, 4 in the R207910 (25 mg/kg 1/7 group), 6 in the R207910 (25 mg/kg 2/7) group, and 3 in the R207910 (25 mg/kg 5/7) group.

Spleen weights and gross lung lesions. At the start of treatment (Day 0), all mice had more than 10 lung lesions and splenomegaly (mean spleen weight, 637 ± 170 mg). After 2 months, the majority of R207910-treated mice had none or fewer than 10 lung lesions and the mean spleen weights for treated groups were significantly lower than pretreatment values ($P < 0.05$).

Colony-forming unit counts in lungs. The mean colony-forming unit count in the lungs was 4.3 ± 0.3 $\log_{10}$ the day after infection and 6.0 ± 0.3 $\log_{10}$ at the start of treatment 2 weeks later (Table 1). After 1 month of treatment, all mice remained culture positive but the mean colony-forming unit counts in all groups were significantly smaller than pretreatment values ($P < 0.05$). The drop in colony-forming unit count was the same for the same total weekly dose, irrespective of the frequency of administration of R207910 (Figure 1). As an example, the bactericidal activity was similar for 25 mg/kg 5/7,

TABLE 1. BACTERIAL COUNTS IN THE LUNGS OF MICE AFTER 1 AND 2 MONTHS OF TREATMENT WITH R207910 GIVEN AT VARIOUS DOSES AND FREQUENCIES IN MURINE TUBERCULOSIS: EXPERIMENT 1

	Lung CFU ($\log_{10}$ ± SD)		
Treatment	Day 0*	Month 1	Month 2
Infected, untreated	6.0 ± 0.3		
Treated control groups			
H 25 mg/kg 5/7		4.0 ± 0.4	3.5 ± 0.7
R 10 mg/kg 5/7		4.1 ± 0.5	2.9 ± 1.3
P 10 mg/kg 1/7		4.4 ± 0.2	2.8 ± 1.1
R207910: 5 d weekly			
J 25 mg/kg 5/7		2.4 ± 0.5	0.4 ± 0.6
J 12.5 mg/kg 5/7		3.2 ± 0.4	2.2 ± 1.2
J 6.25 mg/kg 5/7		4.3 ± 0.5	3.2 ± 0.7
R207910: Twice weekly			
J 50 mg/kg 2/7		2.4 ± 0.6	0.2 ± 0.02
J 25 mg/kg 2/7		3.0 ± 0.4	1.5 ± 0.4
J 12.5 mg/kg 2/7		4.6 ± 0.4	4.3 ± 0.4
R207910: Once weekly			
J 100 mg/kg 1/7		2.8 ± 0.4	0.03 ± 0.1
J 50 mg/kg 1/7		2.9 ± 0.6	1.9 ± 1.1
J 25 mg/kg 1/7		4.5 ± 0.3	3.1 ± 0.8
R207910: Once every 2 wk			
J 100 mg/kg 1/14		3.7 ± 0.3	2.1 ± 0.7
J 50 mg/kg 1/14		4.8 ± 0.4	4.3 ± 0.6

Definition of abbreviations: H: isoniazid; J, R207910; P, rifapentine; R, rifampin.

Colony-forming unit counts are expressed as mean $\log_{10}$ (CFU) ± standard deviation (SD).

* Day 0 = start of treatment.

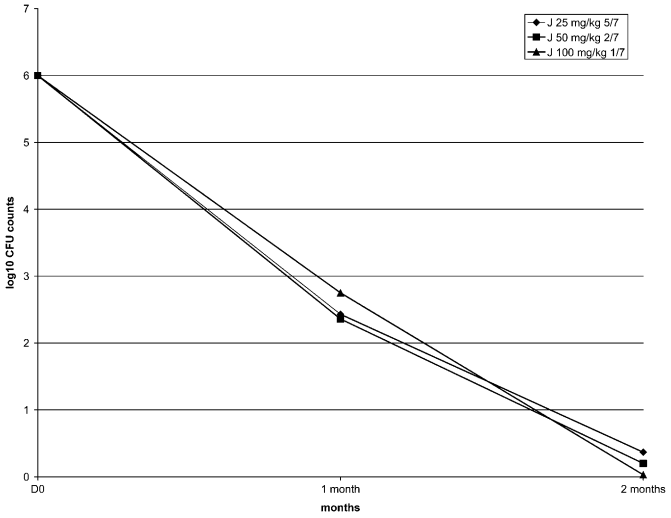

Figure 1. Bacterial counts (log_{10} colony-forming units) in lungs of mice after 1 and 2 months of treatment with R207910 at 25 mg/kg for 5 days per week, 50 mg/kg twice weekly, or 100 mg/kg once weekly in murine tuberculosis (experiment 1). CFU = colony-forming units.

50 mg/kg 2/7, and 100 mg/kg 1/7 (total, 100 to 125 mg/kg/wk). R207910 100 mg/kg once weekly was significantly more active than rifampin 10 mg/kg given 5 days/week or rifapentine 10 mg/kg given once weekly.

Experiment 2

Survival rate. All untreated control mice died between Day 15 and Day 33 after infection. All treatments prevented mortality. One mouse out of 80 (1.25%) died because of a gavage accident in group 4 on Day 30.

Spleen weights and gross lung lesions. At the start of treatment (Day 0), all mice had more than 10 lung lesions and splenomegaly (mean spleen weight, 643 ± 79 mg). After 2 months, the majority of treated mice had none or fewer than 10 lung lesions and the mean spleen weights for treated groups were significantly lower than pretreatment values ($P < 0.05$).

Colony-forming unit counts in lungs. The mean colony-forming unit count in the lungs was 4.0 ± 0.4 log_{10} the day after infection and 6.1 ± 0.6 log_{10} at the start of treatment 2 weeks later. After 1 month of treatment, all mice remained culture positive but the mean colony-forming unit counts in all groups were significantly lower than pretreatment values ($P < 0.01$) (Table 2). After 2 months of treatment, the colony-forming unit count differed significantly between the R207910 monotherapy group and the rifapentine monotherapy group: 0.4 ± 0.7 log_{10} versus 2.3 ± 1.3 log_{10}, respectively. R207910 monotherapy reduced the bacillary load by 5.7 log_{10} after 2 months, that is, by an additional 1.9 log_{10} than rifapentine ($P = 0.007$). After 1 month of treatment, the activity of R207910 was not significantly enhanced by the addition of rifapentine or rifapentine plus moxifloxacin. In contrast, the addition of rifapentine plus isoniazid enhanced the activity of R207910 by approximately 1 log_{10} ($P = 0.01$). However, this difference was no longer significant after 2 months of treatment, when R207910 monotherapy was as active as R207910 plus rifapentine, R207910 plus rifapentine plus moxifloxacin, and R207910 plus rifapentine plus isoniazid ($P > 0.01$). In addition, when comparing the proportion of mice with positive organ culture after 2 months, the combinations did not enhance the activity of R207910 monotherapy.

TABLE 2. BACTERIAL COUNTS IN THE LUNGS OF MICE AND PROPORTION OF MICE WITH NEGATIVE CULTURE AFTER 1 AND 2 MONTHS OF TREATMENT WITH R207910 CONTAINING REGIMENS GIVEN ONCE WEEKLY IN MURINE TUBERCULOSIS: EXPERIMENT 2

Treatment Group	Log_{10} CFU			Proportion of Negative Mice at 2 mo
	Day 0*	Month 1	Month 2	
1: Untreated	6.1 ± 0.6			
2: J		3.2 ± 0.5	0.4 ± 0.7	2/8
3: P		4.7 ± 0.3	2.3 ± 1.3	1/8
4: JP		2.9 ± 0.3	0.4 ± 0.4	1/7
5: JPH		2.1 ± 0.7	0.9 ± 0.8	1/8
6: JPM		2.8 ± 1.4	0.2 ± 0.5	2/8

Definition of abbreviations: H = isoniazid, 75 mg/kg; J = R207910, 125 mg/kg; M = moxifloxacin, 400 mg/kg; P = rifapentine, 15 mg/kg.

Colony-forming unit counts are expressed as mean log_{10} (CFU) ± standard deviation (SD).

* Day 0 = start of treatment.

Experiment 3

Survival rate. All untreated control mice died between Day 5 and Day 35 after infection. Three mice of 10 treated with moxifloxacin monotherapy died of tuberculosis on Day 8. Three mice died of gavage accidents (3.8%): one mouse on Day 7 in group 6 and 2 mice on Day 14, one in group 2, and one in group 3.

Spleen weight and gross lung lesions. At the start of treatment (Day 0), all mice had more than 10 lung lesions and splenomegaly (mean spleen weight, 524 ± 98 mg). After 2 months, the majority of treated mice had none or fewer than 10 lung lesions and the mean spleen weights for the treated groups were significantly lower than pretreatment values ($P < 0.05$) except in the moxifloxacin-treated group (more than 10 lung lesions and no decrease in mean spleen weight).

Colony-forming unit counts in lungs. The mean colony-forming unit count in the lungs was 6.1 ± 0.6 the day after intravenous inoculation, and 7.2 ± 0.5 log_{10} at the start of treatment 2 weeks later (Table 3). As observed in the first and second experiments, R207910 monotherapy reduced the bacillary load by 5 log_{10} after 2 months whereas rifapentine reduced it by 4 log_{10} ($P = 0.005$). Rifapentine plus moxifloxacin and rifapentine plus isoniazid had little additive effect when combined during 2 months with R207910, enhancing the drop in colony-forming unit count by 0.1 and 0.5 log_{10}, respectively

TABLE 3. BACTERIAL COUNT IN THE LUNGS OF MICE, AND PROPORTION OF MICE WITH NEGATIVE CULTURE, AFTER 2 MONTHS OF TREATMENT GIVEN ONCE WEEKLY IN MURINE TUBERCULOSIS: EXPERIMENT 3

Treatment Group	Log_{10} CFU	Proportion of Negative Mice
1: Untreated D0	7.2 ± 0.5	0/20
2: RHZ*	2.2 ± 0.6	0/9
3: J	2.0 ± 0.8	0/9
4: P	3.3 ± 0.6	0/10
5: M	6.4 ± 0.5	0/7
6: JP	1.6 ± 0.9	1/9
7: JPH	1.5 ± 0.8	0/10
8: JPM	1.9 ± 0.7	0/10
9: JPZ	0.2 ± 0.7	9/10

Definition of abbreviations: D0 = Day 0 (start of treatment); H = isoniazid, 25 mg/kg 5 days/week or 75 mg/kg once weekly; J = R207910, 125 mg/kg; M = moxifloxacin, 200 mg/kg; P = rifapentine, 15 mg/kg; R = rifampin, 10 mg/kg; Z = pyrazinamide, 150 mg/kg 5 days/week or 300 mg/kg once weekly.

Colony-forming unit counts are expressed as mean log_{10} (CFU) ± standard deviation (SD).

* Given five times weekly.

($P > 0.05$). In contrast, the mean colony-forming unit count in the lungs of mice receiving R207910 plus rifapentine plus pyrazinamide (0.2 ± 0.7) was significantly smaller than the mean colony-forming unit count in the lungs of mice receiving R207910 alone ($P = 0.0006$), R207910 plus rifapentine ($P = 0.0027$), R207910 plus rifapentine plus moxifloxacin ($P = 0.0008$), or R207910 plus rifapentine plus isoniazid ($P = 0.001$). Moreover, the mean colony-forming unit count in mice treated once weekly with the triple combination of R207910 plus rifapentine plus pyrazinamide was 2 $\log_{10}$ lower than that in mice treated daily with the standard regimen of rifampin plus isoniazid plus pyrazinamide ($P = 0.0009$). When comparing the proportion of mice with negative organ culture, the triple combination of R207910 plus rifapentine plus pyrazinamide was also the only group significantly different from the others. Indeed, 9 of 10 mice were culture negative with this combination whereas in the other groups all mice were culture positive, except a single mouse in the R207910 plus rifapentine group.

DISCUSSION

Although the strong antituberculous activity and long half-life of rifapentine were established years ago, its use in clinical practice is limited by the lack of a companion drug with a long plasma half-life. Once-weekly rifapentine and isoniazid in the continuation phase was found less effective than comparator regimens based on rifampin and isoniazid (11, 12). Indeed, because combination therapy is necessary to prevent the emergence of resistance, treatment of tuberculosis must always include at least two active drugs. When rifapentine is combined with isoniazid in once-weekly regimens, rifapentine remains the only active drug after the clearance of isoniazid, because of the short half-life of the latter (1 to 3 h). This exposes patients to the risk of treatment failure due to the selection of rifamycin-resistant mutants, as was demonstrated in a controlled trial (5, 13). There has been renewed interest in rifapentine since the discovery of moxifloxacin, a fluoroquinolone with high activity against *M. tuberculosis* and exhibiting a plasma half-life of 9 hours in humans. In the murine model of tuberculosis, some rifapentine- and moxifloxacin-containing drug combinations given once weekly are as active as the standard daily regimen rifampin plus isoniazid plus pyrazinamide. Such rifapentine-containing regimens are even more active when given twice weekly (6, 14).

R207910 has two important characteristics favoring its use for intermittent therapy of tuberculosis (*1*): a long half-life (173 h in man, 2 d in mouse) and (*2*) a low proportion of resistant mutants (10^{-7} to 10^{-8}) (7). In a pilot study we evaluated the activity of the daily administration of R207910 in the murine model of tuberculosis (7). At the dose of 25 mg/kg, R207910 reduced the bacillary load by approximately 2.5 to 3.0 $\log_{10}$ CFU per month and was as active as the standard daily regimen of rifampin plus isoniazid plus pyrazinamide. In the present study the bactericidal activity of R207910 was shown to be equivalent when administered (*1*) once weekly at 100 mg/kg, (*2*) twice weekly at 50 mg/kg and (*3*) 5 days/week at 25 mg/kg (2.5 to 3.0 $\log_{10}$ reduction of the bacillary load per month). Thus the bactericidal activity of R207910 correlates with the total weekly dose, irrespective of the frequency of administration. In the current study, a weekly dose of R207910 at 100 to 125 mg/kg exceeded the activity of a once-weekly dose of rifapentine at 15 mg/kg. Moreover, once-weekly monotherapy with R207910 was as active as the standard daily triple-drug regimen of rifampin plus isoniazid plus pyrazinamide.

The addition of isoniazid and rifapentine increased the bactericidal activity of R207910 monotherapy after 1 month of treatment. The speed of bacillary killing is important in the treatment of patients with tuberculosis as it reduces their contagiousness and contributes to the prevention of selection of resistance. However, the most impressive result obtained in this study is the activity of R207910 combined with rifapentine and pyrazinamide. Indeed, this triple-drug combination given once weekly decreased the bacillary load by 7 $\log_{10}$, and resulted in negative lung cultures in 9 of 10 mice after only 2 months of therapy, that is, after only 8 weekly doses. This weekly triple-drug combination was even more active ($P = 0.0009$) than the standard treatment rifampin plus isoniazid plus pyrazinamide given 5 days/week, an activity that is unprecedented for any weekly regimen (10, 15, 16). Indeed, the triple combination of rifapentine plus moxifloxacin plus pyrazinamide must be administered twice weekly and must be preceded by an intensive phase during which the treatment is given daily to obtain the same decrease in bacillary load (14). Interestingly, the triple combination of R207910 plus rifapentine plus pyrazinamide given once weekly displayed a 2-month bactericidal activity equivalent to that of R207910 plus rifampin plus pyrazinamide given 5 days/week obtained in one study (8). Although the present work was not designed to investigate synergism between the antituberculous agents used, the impressive activity of the triple combination of R207910 plus rifapentine plus pyrazinamide that led to a decrease in bacillary load significantly higher than that obtained with the double combination R207910 plus rifapentine, strongly suggests that R207910 and pyrazinamide act synergistically even when given once weekly. A synergistic interaction between pyrazinamide and R207910 was revealed in earlier studies in which both drugs were administered 5 days/week (8). The activity in once-weekly regimens suggests that the rather short half-life of pyrazinamide in mice does not hamper a synergistic interaction. It would be interesting to determine the lowest active dose of pyrazinamide needed in combination studies with the diarylquinoline, as pyrazinamide is rather toxic at the current human dose (17).

It should be determined which once-weekly R207910-containing drug combinations result in acceptable relapse rates in the murine model. Although rifapentine associated with moxifloxacin or isoniazid did not substantially enhance the bactericidal activity of R207910 after 2 months, it is possible that these drugs increase the sterilizing activity and consequently reduce the total duration of therapy. It is indeed established that moxifloxacin increases the sterilizing activity of once-weekly regimens despite having little bactericidal activity when given alone (10, 18). Moreover, isoniazid and moxifloxacin may also be necessary for early bactericidal activity. The pharmacokinetic properties of R207910 and the impressive bactericidal activity of the triple combination of R207910 plus rifapentine plus pyrazinamide suggest the possibility of developing a fully intermittent regimen against drug-sensitive tuberculosis. Such a regimen would significantly increase compliance and facilitate DOT. Relapse experiments should focus on the possible emergence of resistant mutants as this has been the main problem associated with the development of a once-weekly antituberculous regimen in humans.

R207910 could also be tested as a backbone of intermittent treatment against latent tuberculosis. A clinical trial has demonstrated that a 3-month once-weekly regimen containing isoniazid plus rifapentine is as effective, and less toxic, than a 2-month daily rifampin plus pyrazinamide regimen (19). In view of the superiority of R207910 over rifapentine in the mouse model, a shorter regimen could be tested.

There are some limitations to the extrapolation of the present results to the human situation. First, because tuberculosis develops much faster in mice (mice die in less than 2 mo), the mouse model may underestimate efficacy in humans.

Moreover, mice do not develop lung cavities and the spread of the bacilli is hematogenous rather than bronchogenous. For these reasons, we included the standard WHO treatment consisting of rifampin, isoniazid, and pyrazinamide as a control group. Because the activity of this regimen is well established in humans as well as in the murine model, it facilitates interpretation of the results.

A second limitation of our studies is the dose of R207910 that was used. To be predictive of what will happen in humans, the doses used in the mouse model should generate pharmacokinetic parameters similar to those observed in humans. In human volunteers, 400 mg of R207910 given orally was well tolerated and led to a C_{max} of about 5 mg/L and an AUC of 52 mg·hour/L. In mice, oral gavage with R207910 at 25 mg/kg leads to a C_{max} of 1.2 mg/L and an AUC of 19 mg·hour/L. Assuming dose linearity, the expected C_{max} and AUC after a dose of 125 mg/kg should be approximately 6 mg/L and 100 mg·hour/L, respectively (7). Thus the C_{max} obtained in mice treated with 125 mg/kg is comparable to that obtained in humans with 400 mg, and the AUC is comparable to that obtained in humans with 800 mg. Further pharmacokinetic studies in mice and in humans are warranted to precisely delineate the equipotency of once-weekly doses of R207910 in mice and humans.

A third limitation is that rifapentine may induce the metabolism of R207910 in humans and lower its plasma concentrations, similar to what has been observed with rifampin. We do not know whether such drug–drug interaction exists in the murine model.

In conclusion, R207910 displays a similar high bactericidal activity against *Mycobacterium tuberculosis* in mice whether given weekly or daily, provided that the total weekly dose of drug is the same. The triple-drug combination of R207910 plus rifapentine plus pyrazinamide displays unprecedented bactericidal activity in mice, and raises the possibility of developing a new, fully intermittent short-course regimen for the therapy of tuberculosis.

Conflict of Interest Statement: N.V. has been reimbursed by Johnson & Johnson for attending ICAAC. M.I. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.L. is an employee of Tibotec/Johnson & Johnson and has shares in the company. A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.T.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.A is an employee of Tibotec/Johnson & Johnson, has shares in the company, and is coauthor on some patents. The V.J. laboratory received €128,106 in 2007 from Johnson & Johnson for organizing experiments in mice and has been reimbursed by Johnson & Johnson for attending ICAAC.

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